REMARKS

Claims 1-11, 15-27 and 38-58 were previously withdrawn from consideration in response to a restriction requirement. Claims 13, 29 and 30 were previously canceled. Accordingly, claims 12, 14, 28 and 31-37 are currently subject to examination.

Claims 12 and 14 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Cerami, U.S. Patent Application No. 2002/0077271, in view of Liversidge et al., U.S. Patent No. 6,221,400 ("Liversidge"), or Dong, U.S. Patent Publication No. 2002/0071863.

Claims 28 and 31-37 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Cerami, U.S. Patent Application No. 2002/0077271, in view of Liversidge et al., U.S. Patent No. 6,221,400 ("Liversidge"), or Dong, U.S. Patent Publication No. 2002/0071863, and further in view of Davis, U.S. Patent No. 5,278,173 and Johan Boelaert, Biochemical Pharmacology, 61, 1531-1535, 2001).

Rejection of Claims 12 and 14 Under 35 U.S.C. §103(a)

Claims 12 and 14 stand rejected under 35 U.S.C. §103(a) based upon Cerami, U.S. Patent Application No. 2002/0077271, in view of Liversidge et al., U.S. Patent No. 6,221,400 ("Liversidge"), or Dong.

Claims 12 and 14 recite one embodiment of the present invention in which a therapeutically effective amount of an HIV protease inhibitor is administered to a person in need thereof for treatment for malaria. As recited in claim 12, the HIV protease inhibitor is selected from the group consisting of indinavir (IDV), ritonavir (RTV), saquinavir (SQV), nelfinavir (NFV), lopinavir (LPV), amprenavir (APV), fosamprenavir, tipranavir, atazanavir, TMC-114, and combinations thereof. Pharmaceutically acceptable salts of these protease inhibitors may

also be used in the method of amended claim 12. Claim 14 recites a specific embodiment of the invention in which ritonavir is administered at a dose of between about 1 mg per kg of body weight to about 150 mg per kg of body weight. As described in the specification at, for example, paragraphs 0063 and 0064, the HIV protease inhibitors recited in claims 12 and 14 exhibit antimalarial effects. As demonstrated in Examples II and III of the specification, these antimalarial effects are observable in vitro and in vivo.

Cerami describes a wide variety of alkyl aryl carbonyl compounds that react with specific sequences in proteins. Paragraph 0001. Cerami states that the compounds may be used to treat infectious diseases such as HIV infection and malaria. Paragraph 0001. Although the broad description of compounds in Cerami includes hundreds, if not thousands, of compounds, it does not appear that any of the protease inhibitors recited in claim 12 are within the broad description. Moreover, none of the embodiments actually described and tested in Cerami include any of the protease inhibitors recited in claim 12. Indeed, at page 3 of the Office Action, the Examiner states that Cerami "differs from the instant claims only in that Cerami does not include at least one inhibitors of the HIV protease for treating malaria." Thus, the Examiner recognizes that Cerami does not teach or suggest the use of the protease inhibitors of claim 12 for treatment of malaria.

Liversidge is directed to compositions comprising nanoparticulate HIV protease inhibitor drug substances having a cellulosic surface stabilizer. According to Liversidge, the nanoparticulate formulations have an increased rate of dissolution in vitro and an increased rate of absorption in vivo. Liversidge describes the use of the nanoparticulate HIV protease inhibitors for treatment of HIV infections only. Liversidge does not describe or suggest the use of the protease inhibitors for treatment of malaria.

Dong is directed to pharmaceutical compositions comprising liquid antiviral drug formulations in a sustained release dosage forms. Paragraph 0009. The antiviral drug formulations include protease inhibitors. Paragraph 0029. Dong describes the use of the formulation for those in need of antiviral treatment, such as treatment of HIV infection. Dong does not describe or suggest the use of the compositions for anything other than antiviral treatment, and Dong certainly does not describe or suggest the use of the compositions for treatment of malaria.

Cerami does not describe the use of the protease inhibitors of claims 12 and 14 at all, and neither Liversidge nor Dong describe the use of protease inhibitors for treatment of malaria. Although none of the references cited by the Examiner actually describes or suggests the use of protease inhibitors for treatment of malaria, the Examiner nevertheless finds the claimed method obvious in view of the references on the grounds that one skilled in the art, without any suggestion or guidance to do so, would have substituted the protease inhibitors described in Liversidge and Dong for the aryl alkyl compounds of Cerami. This is not a proper obviousness rejection, particularly in the field of technology of the present invention, which is by its nature an unpredictable art. There is nothing in the prior art cited by the Examiner that would have led one skilled in the art to conclude or believe that the protease inhibitors recited in claim 12 would be successful in treating malaria. Indeed, as noted in Cerami at paragraphs 0029 to 0032, malaria has been treated by a variety of regimens due to resistance developed to certain treatments. There is nothing in the references cited by the Examiner that suggests the use of protease inhibitors for the treatment of malaria.

Following the Supreme Court's decision in KSR Intrnational Co. v. Teleflex Inc., 127 S.Ct. 1727 (2007), the Federal Circuit has made clear, particularly in the unpredictable field of

pharmaceuticals and novel uses of pharmaceuticals, that the prior art must provide a reason for one skilled in the art to expect success in a new treatment. In Pharmastem Therapeutics, Inc. v. Viacell, Inc., 491 F.3d 1342, 1364 (2007), which involved a patent on a method for hematopoietic or immune reconstitution of a human using neonatal or fetal blood componenets, the Federal Circuit reiterated that "an invention would not be deemed obvious if all that was suggested 'was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only a general guidance as to the particular form of the claimed invention or how to achieve it.'" See also Eisai Co. v. Dr. Reddy's laboratories, Ltd., 533 F.3d 1353, 1359 (2008)(noting that focus in KSR on "identified, predictable solutions" for obviousness analysis may be difficult hurdle in unpredictable arts because potential solutions are less likely to be predictable).

In this case, the references cited by the Examiner do not even suggest the use of protease inhibitors for treatment of malaria, much less provide any guidance on how to perform or achieve success with the treatment. The references cited certainly do not suggest or provide guidance regarding the use of the protease inhibitors recited in claims 12 and 14 for treatment of malaria. Accordingly, the methods of claims 12 and 14 are not obvious in view of the cited references, and Examiner's rejection of claims 12 and 14 should be withdrawn for at least this reason.

Rejection of Claims 28 and 31-37 Under 35 U.S.C. §103

Claims 28 and 31-37 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Cerami, U.S. Patent Application No. 2002/0077271, in view of Liversidge et al., U.S. Patent No. 6,221,400 ("Liversidge"), or Dong, U.S. Patent Publication No. 2002/0071863, and further in

view of Davis, U.S. Patent No. 5,278,173 and Johan, Biochemical Pharmacology, 61, 1531-1535, 2001).

Claims 28 and 31-37 as amended recite an embodiment of the invention in which a combination of a quinolic compound and an HIV protease inhibitor are administered to a patient in need of treatment for HIV infection, malaria, or both. As recited in amended claim 28, the quinolic compound is selected from the group consisting of chloroquine, hydroxychloroquine, mefloquine, quinine and combinations thereof. The HIV protease inhibitor is selected from the group consisting of indinavir, ritonavir, saquinavir, nelfinavir, lopinavir, amprenavir, fosamprenavir, tipranavir, atazanavir, TMC-114 and combinations thereof. Claims 31-32 recite embodiments of the invention in which a nucleosidic inhibitor of the HIV Reverse Transcriptase (NRTI) compound is also administered. Claims 33-37 recite specific amounts of the quinolic compounds or HIV protease inhibitor in the combinations used in the methods.

As described in the specification at, for example, paragraphs 0047-0050, administration of the combination of an HIV protease inhibitor with an anti-malarial compound such as chloroquine can restore sensitivity to HIV protease inhibitors (PIs) in strains of HIV virus that are resistant to PIs. In addition, use of a quinolic compound in combination with a PI can reduce the effective dose of the PI required to treat the HIV infection. This can decrease the cost of the treatment and reduce possible toxicity associate with administration of PIs.

As further described in the specification at, for example, paragraphs 0051 and 0090-0091, administration of a combination of a quinolic compound, such as chloroquine, with a PI exhibits a synergistic effect in the treatment of *P. falciparum* strains of malaria.

As discussed above, Cerami does not describe the use of protease inhibitors at all, much less describe or suggest the use of a combination of protease inhibitors and quinolic compounds

for the treatment of HIV and malaria. Moreover, while Cerami does refer to the use of a combination of the aryl alkyl carbonyl compounds described in Cerami in combination with anti-malarial compounds for treatment of malaria (Paragraph 0143), Cerami does not describe a combination of protease inhibitors and anti-malarial compounds for any purpose, much less for treatment of HIV or malaria.

As further discussed above, Liversidge and Dong are directed to compositions comprising protease inhibitors for use in treatment of HIV infection. Neither Liversidge nor Dong describe treatment of malaria at all. Moreover, neither Liversidge nor Dong describe, teach or otherwise suggest the combination of quinolic compounds with protease inhibitors for treatment of any disease, much less teach or suggest the use of combinations of the quinolic compounds and protease inhibitors recited in claims 28 and 31-37 for treatment of malaria or HIV.

Davis describes the use of certain anti-malarial compounds, including chloroquine, for treatment of HIV infection. Davis does not describe, teach or suggest the use of HIV protease inhibitors for treatment of malaria at all. Moreover, Davis does not teach or suggest administering a combination of a quinolic anti-malarial with a protease inhibitor for treatment of either malaria or HIV infection as recited in claim 28 as amended, and Davis does not describe or recognize the synergistic effect of the combination in the treatment of malaria or HIV infection.

The final reference cited by the Examiner, Boelaert, "The additive in vitro anti-HIV-1 effect of chloroquine, when combined with zidovudine and hydroxyurea", Biochemical Pharmacology, 2001, Vol. 61, pages 1531-35, does not describe or suggest the combination of a quinolic compound with a protease inhibitor to treat malaria and HIV. Boelaert describes merely an additive effect observed when CQ is combined with zidovudine (AZT), an antiretroviral drug,

and with hydroxyurea. There is no description of the use of a quinolic compound with the protease inhibitors recited in claims 28 and 31-37 as amended, much less any suggestion that such a combination would produce synergistic effects in the treatment of malaria and HIV infection.

In sum, none of the reference cited by the Examiner, either alone or in combination, describe, teach or otherwise suggest the use of a combination of the quinolic compounds and the protease inhibitors recited in claims 28 and 31-37 for the treatment of malaria or HIV infection. As recognized by the Examiner in the prior Office Action, treatment of malaria and HIV infection is unpredictable. The inventor has discovered that certain HIV protease inhibitors are effective in treating malaria, and has also discovered that the combination of certain quinolic anti-malarials in combination with certain protease inhibitors can provide synergistic effects in the treatment of both malaria and HIV infection. As discussed above, the combination of the references cited by the Examiner does not result in the treatment methods in any of claims 12, 14, 28 or 31-37 as amended, and the claims as amended are patentable over the references cited by the Examiner. There is nothing in the references that would lead one skilled in the art to predict the success of the methods for treating malaria or HIV, or that the combinations of quinolic compounds and protease inhibitors would act synergistically to enhance treatment of the diseases. Moreover, there is no guidance provided in the cited references to achieve the success described by the inventor in the application. Accordingly, for at least the reasons given above, the Examiner's rejections under 35 U.S.C. § 103(a) should be withdrawn.

In view of the foregoing remarks, the pending claims are believed to be allowable over the prior art of record. Accordingly, it is respectfully requested that this application be allowed and a Notice of Allowance issued. If the Examiner believes that a telephone conference with

Applicants' attorney would be advantageous to the disposition of this case, the Examiner is cordially requested to telephone the undersigned. If the Examiner has any questions in connection with this paper, or otherwise if it would facilitate the examination of this application, please call the undersigned at the telephone number below.

Because the reasons above are sufficient to traverse the rejection, Applicants have not explored, nor do they now present, other possible reasons for traversing such rejections. Nonetheless, Applicants expressly reserve the right to do so, if appropriate, in response to any future Office Action.

A Petition for a Three Month Extension of Time and the associated fee have been field herewith, extending the time to respond until October 16, 2008. No additional fee is believed to be required. However, if any fee is required, or otherwise if necessary to cover any deficiency in fees already paid, authorization is hereby given to charge our Deposit Account No. 50-3569.

Respectfully submitted,

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